The Neural Correlates of Working Memory Training in Typically Developing Children

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Abstract

Working memory training improves cognitive performance on untrained tasks; however, little is known about the underlying neural mechanisms, particularly in childhood where neuroplasticity may be greatest. The neural correlates of working memory training were investigated in 32 typically developing children aged 10-14 years (19 girls and 13 boys; Devon, UK) using a randomised controlled design and multi-modal MRI. Training improved working memory performance and increased intrinsic functional connectivity within the dorsal attention network. Furthermore, improvements in working memory were associated with greater recruitment of the left middle frontal gyrus during a complex span task. The repeated engagement of fronto-parietal regions during training may increase their activity and functional connectivity over time, affording greater attentional control on working memory tasks.

Introduction

Working memory, the ability to retain and manipulate information over a short period of time (Baddeley and Hitch, 1994), is considered a core executive function (Miyake et al., 2000), is associated with a wide range of cognitive skills (Barrett et al., 2004), and predicts children's academic outcomes (Alloway and Alloway, 2010). For these reasons, working memory has been a common target for training interventions. Meta-analyses have repeatedly shown that training improves performance on untrained working memory tasks (Melby-Lervåg et al., 2016; Sala and Gobet, 2017a; Schwaighofer et al., 2015; Shipstead et al., 2012; Soveri et al., 2017). It has been suggested that training, through repeated and prolonged practice on working memory tasks, leads to neuroplastic changes that support increased cognitive capacity (Klingberg, 2010). However, this assumption has not been extensively tested and, on the contrary, evidence for improvements in other domains associated with working memory capacity, such as reasoning and academic attainment, is very limited (Aksayli et al., 2019; Sala and Gobet, 2017b, 2017a, 2019; Simons et al., 2016). The purpose of this investigation was to examine the structural and functional neural correlates of working memory training in typically developing children using magnetic resonance imaging (MRI).

As neurodevelopment depends partly on learned skills (Johnson, 2011), the neural changes occurring from natural development of working memory may share some commonalities with neural changes from training. Mature working memory in adulthood activates a bilateral fronto-parietal network including core regions in the dorsolateral prefrontal cortex, middle frontal gyrus, and superior parietal lobe (Rottschy et al., 2012). However in childhood, working memory is associated with more distributed activity, which is reduced in fronto-parietal regions compared to adults (Geier et al., 2009) and increased in the caudate and thalamus (Scherf et al., 2006). On-task fronto-parietal activity increases in childhood and is associated with increases in working memory capacity (Klingberg et al., 2002). Furthermore,

as children's working memory matures, brain activity becomes more localised to core working memory regions and more functionally integrated with regions involved in response preparation and execution (Scherf et al., 2006). These findings follow common neurodevelopmental trends in resting brain function (Fair et al., 2013; Satterthwaite et al., 2013), which may be mediated by changes in brain structure (Johnson 2011). Specifically, functional specialisation in neighbouring regions may occur due to a reduction in local grey matter volume through synaptic pruning, whilst integration between remote neural populations may occur through increased myelination in white matter tracts (Johnson 2011).

The evidence for training-related changes in children's task-related brain activity is currently mixed and limited to three published functional Magnetic Resonance Imaging (fMRI) investigations in children with cognitive and behavioural difficulties. Two pilot studies reported broad changes in fronto-parietal activity when children were engaged in a visual span task: activity increased following Cogmed, a commercially available five week training programme on 11 span tasks (Klingberg et al., 2005), in adolescents with ADHD (Stevens et al., 2016), whereas it decreased following four hours of training on three span tasks in children born very preterm (Everts et al., 2017). Increased activation following training may suggest greater neuronal recruitment, whereas decreased activation may suggest greater efficiency from a more precise neural response (Kelly et al., 2006), akin to specialisation in neurodevelopment. However, interpretation of these mixed findings is significantly limited as neither study compared the effects to a control group. The only controlled investigation in children found that Cogmed was not associated with brain activation changes on an n-back task in children born extremely preterm or extremely low birthweight (Kelly et al., 2020); however, this may be because children in this sample showed no behavioural improvements from training and/or because the task was relatively distal to training (Anderson et al., 2018). Due to limitations in

the previous literature, it is currently unclear whether the improvements on working memory tasks after training are associated with a change in children's task-related brain activity.

Meta-analyses of adult working memory training studies have provided more consistent evidence for activation changes in fronto-parietal regions as well as the striatum. A meta-analysis of eight controlled studies reported decreased activity in the right middle frontal gyrus and right inferior parietal lobe, and affected activity in the putamen (Li et al., 2016). Yet this also included studies with brief practice, which are less typical for cognitive training programmes and have more often been associated with activation decreases (see Klingberg, 2010). A more recent meta-analysis of 26 studies also reported decreased activation in the right posterior parietal cortex but increased frontal activations (Salmi et al., 2018). Although no direct analysis was performed, activations compared to perceptual-motor training (as a control) and activations associated with longer training periods (>2 weeks) were consistent in the right dorsolateral prefrontal cortex, the right frontal eye field, and the bilateral insula. Thus the longer training periods adopted in commercially available working memory training programmes for children, such as Cogmed, may be associated with activation increases, particularly in fronto-parietal regions implicated in working memory.

Training effects may also operate at the level of regional interactions in networks that govern cognitive processes (van den Heuvel, 2010). One controlled investigation has previously examined how working memory training affects functional connectivity in typically developing children (Astle et al., 2015). This magnetoencephalography (MEG) study found that Cogmed improved working memory performance and increased functional connectivity between the right fronto-parietal network and left lateral occipital cortex, compared to non-adaptive training. Furthermore, improvements in working memory across groups correlated with increased connectivity within the dorsal attention network and between the dorsal attention network and left inferior temporal cortex. Similar findings were reported in a trial of

21 children born extremely preterm using fMRI (Tseng et al., 2019); although these results did not survive correction for multiple comparisons, trends suggested that Cogmed increased functional connectivity within the dorsal attention and default mode networks, compared to non-adaptive training. It has been suggested that the repeated and demanding co-activation of fronto-parietal regions during training may increase functional connectivity between them and afford greater attentional capacity (Astle et al., 2015). Neurofeedback studies have provided some support for this notion: in the absence of external cognitive demands, regulating activity in the dorsolateral prefrontal cortex has been shown to increase local activity, fronto-parietal connectivity, and working memory performance (Shen et al., 2015; Zhang et al., 2013, 2016).

Finally, it is possible that changes in brain structure may underlie behavioural improvements observed in working memory training. Only one study has examined whether training alters grey matter volume in childhood (Kelly et al., 2020). In 48 children born extremely preterm, children that received Cogmed showed increased volume in the left lateral occipital cortex compared to non-adaptive training, although this did not survive correction for age. The absence of an effect should be treated with caution as there was no behavioural effect of training in this sample, as previously mentioned (Anderson et al., 2018). The findings in adults are similarly equivocal: one study reported broadly increased fronto-parietal volume but only compared to a passive control group (Takeuchi et al., 2013), whereas a study on mental arithmetic training reported reduced fronto-parietal volume compared to an active control group (Takeuchi et al., 2011), and another study reported no significant change compared to an active control group (Metzler-Baddeley et al., 2016). Thus, the possible effects of training on children’s grey matter volume are currently unclear.

The Present Study

Current evidence suggests that working memory training in childhood may be associated with changes in fronto-parietal function. However, controlled investigations of training-related neuroplasticity in typical development are currently limited to one sample of 33 children, where task-related activity and brain structure were not investigated (Astle et al., 2015). Importantly, cognitive and neural plasticity may be greatest in childhood, and particularly in typically developing children, where larger training effects have been observed (Jolles and Crone, 2012; Melby-Lervåg and Hulme, 2013), possibly when neural systems are less specialised and have the greatest propensity to change (Wass, 2015; Wass et al., 2012). It is unclear whether the training effects on brain structure and function reported across studies are reliable, as there is a paucity of controlled studies. Furthermore, it is unclear whether alterations in activity, connectivity, and structure occur concurrently as few investigations have examined neural change across multiple domains. The present study will examine whether adaptive Cogmed working memory training in typically developing children is associated with changes in brain activation on a simple and complex span task, resting-state functional connectivity, and grey matter volume, in comparison to non-adaptive control training. The study provides novel and valuable insights into multiple levels of training-dependent neuroplasticity in childhood. This is not only vital to understanding the mechanisms of cognitive training and its potential efficacy in educational and clinical settings, but also informs on the neurodevelopment of working memory in highly controlled settings.

Method

Participants

Data are presented for 32 children (19 girls and 13 boys) that completed the training and final assessments with a mean age of 12 years and 2 months (*SD* = 1.22 years). An additional 18 children did not complete the training and final assessments (see Figure S1 for details of drop outs and missing data). Participants were recruited from Devon, UK, and the majority were White British (95% in similar studies). The final sample included 17 children in the Cogmed adaptive training intervention group and 15 children in the non-adaptive training control group. At baseline, there were no significant differences between the two conditions in IQ working memory capacity, age, or gender (see Table 1).

Table 1

Baseline Characteristics of the Final Sample.

	Control (n=15)	**Cogmed (n=17)**	***t*(30)**	***p***
	Mean (SD)	**Mean (SD)**		
Age (years)	11.9 (1.15)	12.37 (1.27)	1.1	0.281
IQ	116.07 (14.36)	112 (13.28)	0.83	0.412
AWMA	107 (8.34)	108.28 (7.43)	0.46	0.649
Dot Matrix accuracy	0.72 (0.12)	0.73 (0.09)	0.28	0.779
Odd-One-Out accuracy	0.78 (0.14)	0.82 (0.09)	0.97	0.342

Note. Scores on the Dot Matrix and Odd-One-Out indicate proportion of correct responses.

Design and Procedure

Children and parents/guardians were informed that the aim of the study was to compare two computerised cognitive training programmes. Following baseline assessment, 50 children were randomly allocated to receive either adaptive or non-adaptive working memory training in equal numbers (see Figure S1 CONSORT Flow Diagram). Two children were excluded before randomisation because they could not tolerate the MRI scanner. Parents/Guardians and

children were instructed on how to use their respective training programme and they practised for approximately 10 minutes until they were confident of how they would login and use the programme at home. Training support was offered for all participating children by certified Cogmed coaches, who sent weekly emails and discussed any relevant issues. A parent/guardian also agreed to be the child's training aide, which involved organising training times, managing rewards, and offering encouragement. Training aides were given guidance on how best to support their child's training. Children were given instructions for the training tasks and a booklet to timetable their training sessions, record their goals, and acknowledge mutually agreed rewards with their parent/guardian. The booklet also included a training agreement that the child, training aide, and coach were requested to sign. Training was completed for approximately 45 minutes a day, five days a week, for five weeks and all participating children were instructed to complete 20-25 training sessions in accordance with the Cogmed protocol. Children were rewarded with an item of stationery for every five sessions completed and a £20 Amazon voucher on completion of the whole programme. At the end of the study, children who were assigned to the control group were offered a free license to use Cogmed in their own time.

Working Memory Training

Cogmed RoboMemo included a battery of 11 short-term and working memory tasks with visuospatial and verbal stimuli (Klingberg et al., 2005). The tasks required recalling a sequence of spatial locations in order, tracking and recalling a sequence of moving spatial locations or objects, reordering and recalling a sequence of spatial locations, recalling a sequence of digits in reverse order, and recognising a sequence of letters. Each session lasted approximately 45 minutes with breaks and involved training on eight tasks for approximately

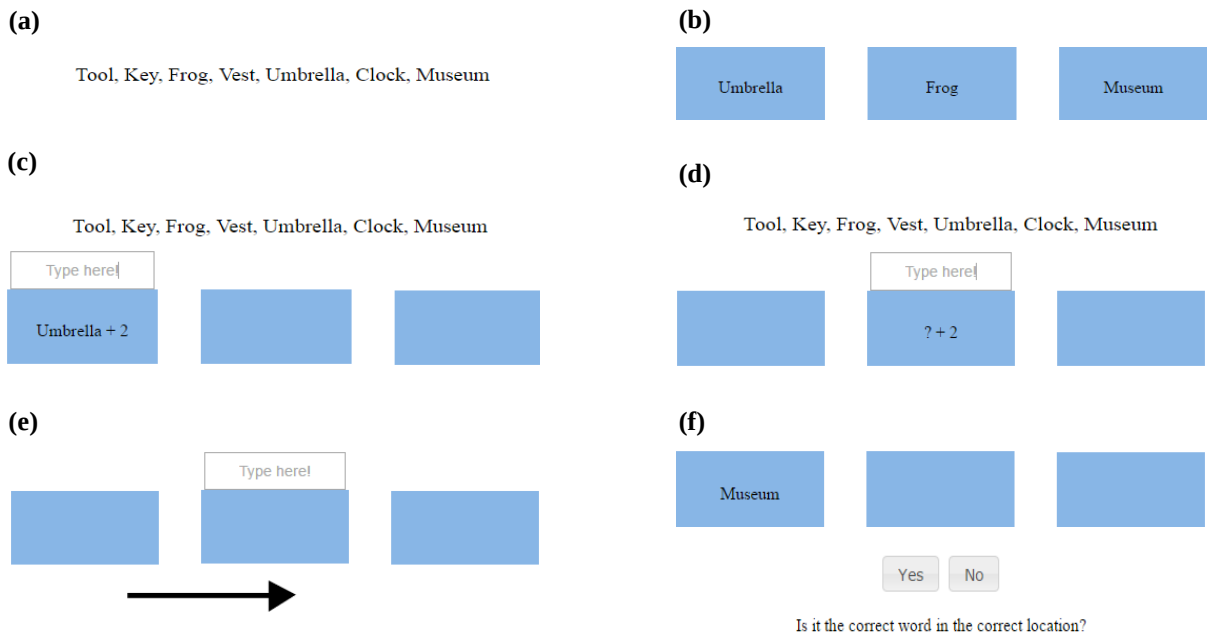
15 trials each. The difficulty of the training tasks adapted on a trial-by-trial basis according to the individual's performance. The complexity of the stimulus sequence or the number of items to remember would increase following successful responses, whereas they would decrease following incorrect responses. To control for time spent training, the number of trials adapted to an individual's processing time and current span level, where fewer trials were presented for children training at a higher span and more trials were presented for children training at a lower span. Cogmed included a difficulty level meter, high scores, audio and verbal feedback, and a reward game 'Robo Racing', which children could play for a few minutes at the end of a session depending on performance.

Children assigned to non-adaptive working memory training practised an online verbal updating working memory task (Roberts et al., 2021). This control task was chosen because it shares a number of characteristics with the non-adaptive version of Cogmed, which was discontinued shortly before the commencement of the study. At the beginning of each session, children were first required to memorise a list of seven words. Their memory was then assessed on a cued and free recall test and children could only proceed to the updating training after perfect performance. On each trial of the training task, three words from the original list were presented in three separate boxes for 5s (see Figure 1). Children were then required to update their memory of the words in accordance with two consecutive updating sub-tasks, which were randomly selected without replacement from a choice of three (see Figure 1: d-f). The sub-tasks either required replacement of a target word with one that was one or two words further down the original list (Figure 1: d-e), or replacement of a target word with one from the other boxes (Figure 1: f). In the event that the sub-tasks indicated replacement of a word beyond the end of the list, children were instructed to start again at the beginning of the list. Finally, a word from the original word list was presented in one of the boxes and children were asked if it was the correctly updated word for that box. Children were given 5 seconds to respond 'Yes' or

'No', before it was marked incorrect. Half of the trials required a 'Yes' response and half of the trials required a 'No' response. Difficulty was fixed throughout. Children were required to remember three words and had to perform two consecutive updating tasks on each trial.

Figure 1.

Components of the non-adaptive control updating task.



Note. (a) a new word list was learnt at the beginning of each training session and was present during the updating sub-tasks; (b) at the start of the trial, three words were presented in Boxes 1-3 (left to right) for 5s; (c) updating sub-task 1 presented '+1' or '+2' next to one of the words, indicating replacement with the word that is one or two forward in the original word list - here the contents of Box 1 ('Umbrella') should be replaced with the word that is two forward in the list ('Museum'); (d) updating sub-task 2 presented a question mark, which masked a word in one of the boxes, and '+1' or '+2', indicating replacement with the word that is one or two forward in the word list - here the contents of Box 2 ('Frog') should be replaced with the word that is two forwards ('Umbrella'); (e) updating sub-task 3 required replacement of the contents of Box 2 ('Umbrella') with the contents of Box 1 ('Museum'), as indicated by the arrow; (f) following two updating sub-tasks, a word was shown in one of the boxes and children decided if it was the correct word.

Measures

Standardised assessments were administered by trained researchers who were unaware of the child's group assignment. Working memory was assessed before and after training using

eight span tasks from the Automated Working Memory Assessment (AWMA; Alloway, 2007). This included two measures of verbal storage (Digit Recall and Word Recall), two measures of verbal working memory (Backwards Digit Recall and Listening Recall), two measures of visuospatial storage (Mazes Memory and Block Recall), and two measures of visuospatial working memory (Mr. X and Spatial Span). There is good test-retest reliability for these measures ranging from r = 0.64-84 (Alloway et al., 2006). There is high agreement between simple and backward/complex span tasks in children (Alloway et al., 2006), suggesting that they measure the same underlying sub-processes (see Unsworth and Engle, 2007). As such, performance across the tasks was averaged for each individual to form an overall composite score of working memory, as in previous studies (Astle et al., 2015; Jones et al., 2019).

IQ was also assessed to characterise the sample at baseline using the two sub-tests version (FSIQ-2) of the Wechsler Abbreviated Scale of Intelligence-II (WASI-II; Wechsler, 2011). This included a measure of crystallised intelligence (Vocabulary) and a measure of fluid intelligence (Matrix Reasoning). The FSIQ-2 has excellent internal consistency ($\alpha = 0.93$), test-retest reliability (r = 0.87-0.95), and interrater reliability (McCrimmon and Smith, 2013).

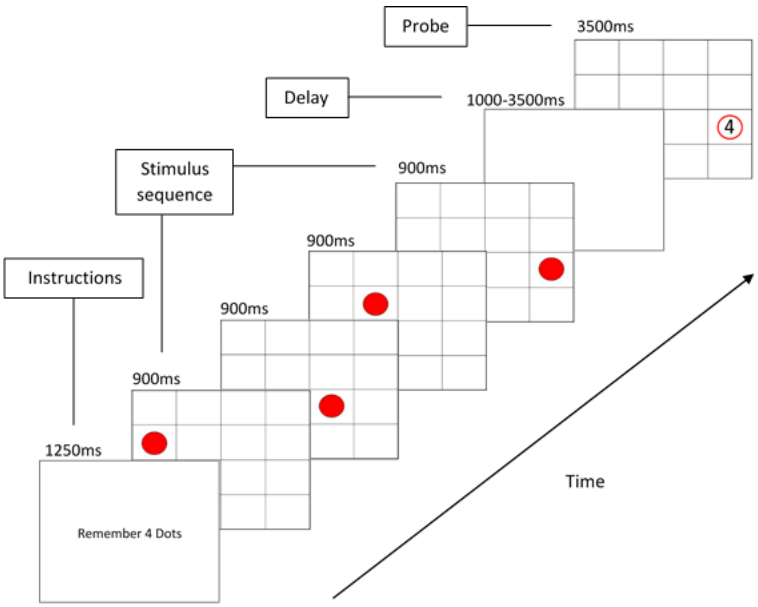
fMRI Tasks

The Dot Matrix was a simple span task (see Figure 2) adapted from the AWMA (Alloway, 2007) and is comparable to tasks used in other neuroimaging investigations of Cogmed in adults (Brehmer et al., 2011; Olesen et al., 2004; Westerberg and Klingberg, 2007). Four to six red dots were sequentially presented on a 4x4 grid for 900ms each, with no inter-stimulus interval (ISI). The dot locations were pre-randomised, meaning that they were consistent for each participant and each session, and they were never repeated within a trial. After a randomised delay of 1000-3500ms, a probe dot was presented in the grid with a number

from one to six within it, indicating the serial order of the probe. Participants were required to indicate if the probe was in the correct location and order as one of the previously presented dots by pressing the left button for 'yes' and right button for 'no'. The inter-trial interval was randomised between 2000-4000ms. The task consisted of 54 trials across two runs, 18 of each span length (4, 5, and 6). Half of the trials required a correct response and half required an incorrect response, approximately half of the incorrect trials presented lures (n = 13), i.e. probes that were in the same location as a previously presented dot but in a different order.

Figure 2.

Procedure and timings for the Dot Matrix task



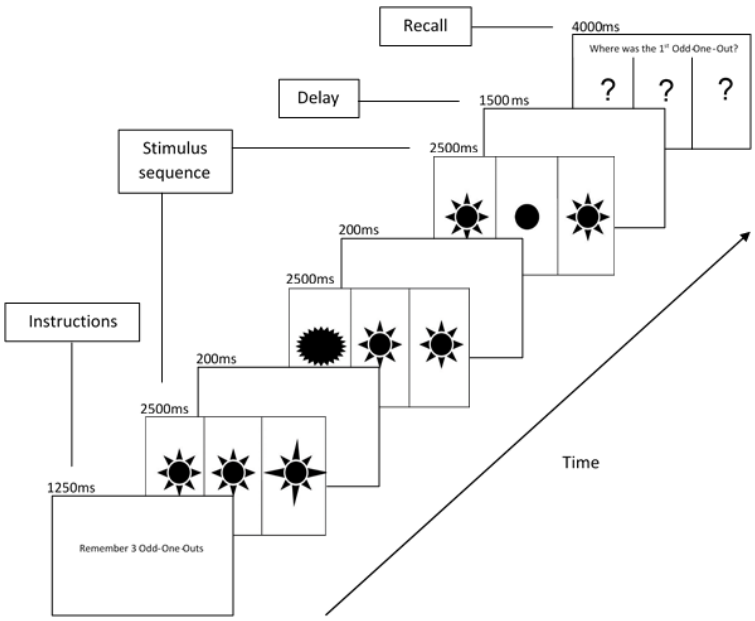
Note. An example of a correct probe trial at span four is presented. At the start of each trial, instructions regarding how many stimuli to remember were briefly presented for 1250ms. In the encoding phase, four to six red dots were displayed sequentially on a 4x4 grid for 900ms per stimulus. The stimulus sequence was followed by a randomised delay between 1000 and 3500ms. Finally, a probe was presented for 3500ms and children judged if it was presented in the same location and order as one of the dots from the sequence

The Odd-One-Out was a complex span task (see Figure 3) also adapted from the AWMA (Alloway, 2007) but has never been used before in published neuroimaging investigations of working memory training. Three to five sets of adjacent shapes were presented sequentially for 2500ms with a 200ms ISI. Each set contained three shapes, two were

the same and one was different or ‘odd’. After a 1500ms delay, children were asked to recall the position of one of the odd-one-outs by pressing the appropriate ‘left’, ‘middle’ or ‘right’ button within 4000ms. This was indicated in text by reference to the 1st, 2nd, 3rd, 4th, or 5th odd-one-out from the sequence. The inter-trial interval was randomised between 1800-4200ms. The task consisted of 48 trials across three runs, 16 of each span length. Correct responses were equally distributed across the three locations. Both fMRI tasks were programmed in E-Prime 2.0 (Schneider et al., 2002).

Figure 3.

Procedure and timings for the Odd-One-Out task.



An example of a trial at span three is presented requiring retrieval of the position of the first stimulus. At the start of each trial, instructions regarding how many stimuli to remember were briefly presented for 1250ms. In the encoding phase, three to five stimuli were presented for 2500ms each with a 200ms ISI. Each stimulus consisted of three adjacent shapes; two were identical and one was different, i.e. the odd-one-out. The stimulus sequence was followed by a 1500ms delay. Finally, children had 4000ms to recall the position of one of the odd-one-outs presented in the sequence.

MRI Acquisition

Functional images were acquired using a 1.5T Phillips Gyroscan magnet, equipped with a Sense coil. A T2*-weighted echo planar sequence was used (TR=3000ms, TE= 45ms, flip angle 90º, 35 transverse slices, 2.5 x 2.5 x 3.5mm). Participants completed one scanning session

before training and one after training. Each session included two runs of the Dot Matrix task, three runs of the Odd-One-Out task, one run of resting-state, and a structural scan. One hundred and twenty six scans were collected for each run of the Dot Matrix, 106 scans were collected for each run of the Odd-One-Out, and 120 scans were collected for the resting-state. The standard volumetric anatomical MR image was acquired using a 3D T1-weighted pulse sequence (TR = 25ms, TE = 4.2ms, flip angle = 30˚, 0.9 x 0.9 x 0.9mm).

fMRI Activation Analysis

The functional images were analysed using SPM12 (www.fil.ion.ucl.ac.uk/spm). The images were corrected for acquisition order, realigned to the first volume and resliced to correct for motion artefacts. Spatial normalisation was performed by coregistering the mean image created from the realigned images to the structural T1 volume. The images were then spatially normalised into the stereotactic space of the Montreal Neurological Institute (MNI). The spatial transformation was applied to the realigned T2* volumes that were spatially smoothed using a Gaussian kernel of 8mm full-width half maximum. Data were high-pass filtered (128s) to account for low frequency drifts. The Blood-Oxygen-Level Dependent (BOLD) response was modelled by a canonical hemodynamic response function (HRF) and the six head movement parameters were included as covariates. Participants with excessive head movements or substantial artefacts were excluded from each fMRI analysis in a casewise manner. Data acquired for the encoding phase of correct trials were contrasted with the implicit baseline. First-level linear contrasts of parameter estimates for each voxel before and after training were taken to the second-level and a random effects analysis was performed. Activation over time was contrasted between each training condition.

The bilateral middle frontal gyrus (MFG) and superior parietal lobe (SPL) were selected a priori as Regions of Interest (ROI) from the Automated Anatomical Labelling atlas (Tzourio-Mazoyer et al., 2002). These regions have previously been associated with activation changes following working memory training (Jolles et al., 2012; Stevens et al., 2016) and adults (Li et al., 2015; Olesen et al., 2004; Westerberg and Klingberg, 2007). The four ROIs were analysed in two ways. First, group differences in mean activation change within each ROI were analysed in the Marsbar toolbox (Brett et al., 2002) using a Bonferroni correction for multiple comparisons ($p < 0.0125$). Second, clusters of activation change were examined within an explicit mask of the bilateral MFG & SPL using a cluster-forming height threshold of $p < 0.005$ (uncorrected). Finally, whole brain analyses were conducted using a cluster-forming height threshold of $p < 0.001$ (uncorrected). Statistical significance was inferred when cluster extent exceeded that expected by chance (Family-Wise Error [FWE] $p < 0.05$) in Monte-Carlo nonparametric simulations of images with equal smoothness (3dClustSim, AFNI). FWE-corrected critical cluster sizes were 70 for the ROI mask and 111 for the whole-brain. Activation coordinates were transformed from normalised MNI space to Talairach space using the 'icbm2tal' tool (Lancaster et al., 2007) to locate the site of activations in relation to the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988).

Functional Connectivity Analysis

Functional connectivity analysis was completed within Conn, version 18a (Whitfield-Gabrieli & Nieto-Castanon, 2012). Pre-processing of the resting-state fMRI was completed using the default Conn pipeline, which implements the same pre-processing steps in SPM12 as outlined for the task-based fMRI above. Identification of global mean intensity and motion outliers was also performed using an automatic artefact detection tool

(http://www.nitrc.org/projects/artifact_detect/). Denoising of physiological and motion artefacts included confound regression of six head movement parameters and their first derivatives, motion/global signal outliers, 10 components estimated from the white matter and cerebrospinal fluid using the aCompCor method (Behzadi et al., 2007), a linear trend, and a band-pass filter 0.008-0.09Hz.

The ROI analyses of the functional connectivity data were conducted using canonically defined resting-state fronto-parietal networks, as in Astle and colleagues (2015). Two fronto-parietal networks of interest were selected within Conn, which uses data from the Human Connectome Project (Van Essen et al., 2013); the fronto-parietal network comprised of the bilateral lateral prefrontal cortex and posterior parietal cortex, and the dorsal attention network comprised of the bilateral frontal eye fields and intraparietal sulci. Four ROI to ROI analyses were conducted for each network, which included: the left MFG and ipsilateral SPL, the right MFG and ipsilateral SPL, the contralateral MFGs, and the contralateral SPLs. A Bonferroni correction for multiple comparisons was applied to the analysis of each network ($p < 0.0125$).

Voxel-Based Morphometry

Voxel-based morphometry (VBM) was used to examine whether Cogmed was associated with changes in regional grey matter volume, compared to the control group. The T1 structural images were analysed using the DARTEL package (Ashburner, 2007) in SPM12 (www.fil.ion.ucl.ac.uk/spm). The pre- and post-training images were initially co-registered to produce an average image and a divergence image, taking into account the individual difference in time between the scans. The average images were segmented, and the resulting grey and white matter images were spatially aligned using DARTEL. The template and flow

fields from DARTEL were used to spatially normalise the divergence images to MNI space, which were then smoothed using a Gaussian kernel of 10mm full-width half maximum.

As the literature is equivocal regarding the effects of working memory training on grey matter volume no regions of interest were selected a priori. Only exploratory whole-brain analyses were conducted at a significance threshold of $p < 0.001$ (uncorrected) and a minimum of 20 contiguous voxels. Activation coordinates were transformed from normalised MNI space to Talairach space using the 'icbm2tal' tool (Lancaster et al., 2007) to locate the site of activations in relation to the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988).

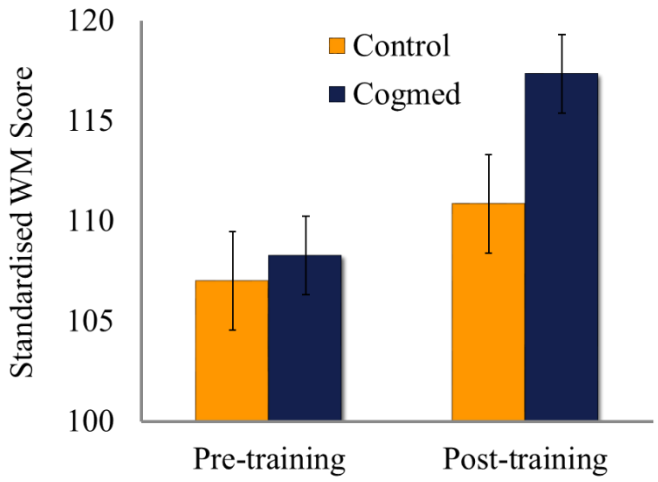
Results

Behavioural Outcomes

Related samples t-tests showed that average scores on the eight working memory tasks significantly increased over time for the Cogmed group, Δ +9.06, $t(16) = 5.83$, $p < 0.001$, and for the Control group, Δ +3.84, $t(14) = 3.13$, $p = 0.007$. A mixed ANOVA of the interaction time (pre-training vs post-training) * group (Cogmed vs Control) showed that working memory scores increased significantly more in the Cogmed group compared to the Control group, $F(1, 30) = 6.7$, $p = 0.015$, $\eta_p^2 = 0.188$ (see Figure 4).

Figure 4

Working Memory Scores Pre- and Post-training for the Two Groups.



Note. Error bars are 95% confidence intervals with a within-subjects adjustment (Morey, 2008).

Resting-State Functional Connectivity

Within the dorsal attention network, the Cogmed group showed significantly increased functional connectivity between the left and right intraparietal sulci, relative to the Control group (p = 0.005 uncorrected; see Table 2). Furthermore, functional connectivity of the left and right intraparietal sulci was associated with improvements in working memory across both groups, $t(26) = 2.1$, $p = 0.046$ (uncorrected), although this did not survive correction for multiple comparisons across the four connections ($p > 0.0125$). Within the lateral fronto-parietal network, the Cogmed group showed no significant changes in functional connectivity relative to the Control group (all $p > 0.104$ uncorrected, see Table S1).

Table 2.

Group comparison of functional connectivity within the dorsal attention network over time.

Seed Regions	T(26)	*p*
Left FEF – Left IPS	0.82	0.419
Left FEF – Right FEF	-0.19	0.853
Right FEF – Right IPS	1.75	0.092
Right IPS – Left IPS	3.11	**0.005***

Note. Comparison of Cogmed-Control, positive values indicate greater increase in functional connectivity in the Cogmed group. FEF = frontal eye field, IPS = intraparietal sulcus. *$p < 0.0125$

Task-based fMRI

Odd-One-Out

Mean activation in the left middle frontal gyrus increased in the Cogmed group relative to the Control group, but this was not significant after correction for multiple comparisons across ROIs (see Table 3).

Table 3

Group Comparison of Mean ROI Activation on the Odd-One-Out Task over Time

ROI	Contrast	*T*(27)	*p*
Left Middle Frontal Gyrus	1.81	1.94	0.032
Right Middle Frontal Gyrus	0.46	0.47	0.321
Left Superior Parietal Lobe	-0.01	-0.01	0.506
Right Superior Parietal Lobe	-0.40	-0.53	0.701

Note. Positive contrast values indicate a greater increase in mean ROI activation in the Cogmed group compared to the Control group. *p* (uncorrected). *$p < 0.0125$

As both groups performed working memory training and the samples were small, power may have been limited to detect a group difference. Investigating the association between changes in working memory performance and activation change across both groups may be a more sensitive approach (Astle et al., 2015). A regression analysis revealed that improvements

in working memory were significantly associated with increased mean activation of the left middle frontal gyrus, $t(28) = 3.61$, $p < 0.001$ (uncorrected, see Table 4 and Figure 5). This was also significant within the Cogmed group, $t(15) = 2.81$, $p = 0.007$ (uncorrected), but not the Control group, $t(12) = 1.17$, $p = 0.134$ (uncorrected; see Tables S5 and S6).

Table 4

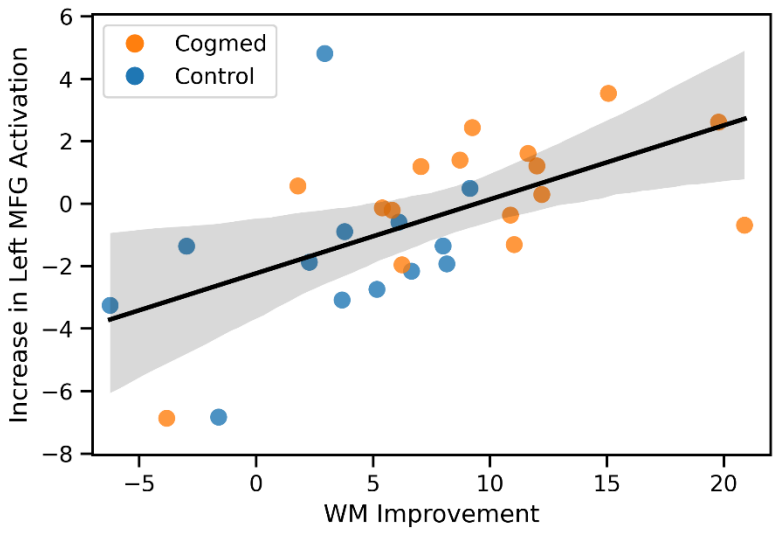
Association between Working Memory Improvements and Mean ROI Activation on the Odd-One-Out Task over Time

ROI	Contrast	*T*(28)	*p*
Left Middle Frontal Gyrus	0.24	3.61	**< 0.001***
Right Middle Frontal Gyrus	0.16	2.27	0.016
Left Superior Parietal Lobe	0.09	1.35	0.093
Right Superior Parietal Lobe	0.07	1.27	0.107

Note. Positive contrast values indicate a positive association between mean ROI activation and improvements on the AWMA across both groups. *p* (uncorrected). *$p < 0.0125$

Figure 5

Association between Working Memory Improvements and Left Middle Frontal Gyrus Activation on the Odd-One-Out Task over Time



Note. WM = Working Memory, MFG = Middle Frontal Gyrus.

We also examined whether there were significant clusters of voxels that showed a change in activation for the Cogmed group relative to the Control group. Exploratory analyses revealed small clusters of increased activation in the bilateral middle frontal gyri in the Cogmed group, relative to the Control group (see Table S2 & Figure S2). However, no clusters significantly exceeded cluster size expected by chance in simulated images of the ROI mask (k > 70) or whole brain (k > 111; see Table S3 & Figure S3).

Dot Matrix

Cogmed did not increase mean activation in the middle frontal gyri or superior parietal lobes, relative to the Control group (all $p > 0.419$ uncorrected). Furthermore, working memory improvements were not significantly associated with change in mean activation of the ROIs, across both groups (all $p > 0.093$ uncorrected). No significant clusters were detected in the ROI mask (k > 70) or whole brain (k > 111, see Table S4).

Grey Matter Volume

There were no significant changes in grey matter volume in the Cogmed group over time, relative to the Control group. Exploratory analyses yielded no clusters greater than 20 contiguous voxels.

Discussion

We examined the structural and functional neural correlates of working memory training in typically developing children. A significantly larger increase in working memory performance was observed in the adaptive training group (Cogmed), relative to the non-

adaptive training group (Control). This was accompanied by changes in brain function but not structure. Specifically, adaptive working memory training significantly increased functional connectivity within the dorsal attention network compared to non-adaptive control training. Furthermore, the improvements in working memory after training were significantly associated with greater engagement of the left middle frontal gyrus on a complex span task (the Odd-One-Out).

Consistent with previous evidence, we observed that working memory training was associated with a large increase in typically developing children's average performance across a range of working memory tasks, relative to control training (Astle et al., 2015; Jones et al., 2019; Sala and Gobet, 2020). The mechanisms of behavioural improvements in working memory as a result of training are still debated. The prolonged mismatch between external demands and current capacity limits during training may induce a neuroplastic change that affords greater capacity (Klingberg, 2010; Lövdén et al., 2010). However, contemporary evidence increasingly suggests that transfer is narrow and limited (Gathercole et al., 2019; Rennie et al., 2021). Transfer may instead depend upon the degree to which the training and transfer tasks share the same high-order cognitive routines for effective performance (Gathercole et al., 2019).

Working memory training significantly increased functional connectivity within the dorsal attention network between the bilateral intra-parietal sulci, compared to non-adaptive training. Furthermore, increased functional connectivity between the intra-parietal sulci appeared to be associated with behavioural improvements in working memory across both groups, although this did not survive correction for multiple comparisons. This corresponds well with the only other controlled investigation in children, which also reported greater resting-state MEG functional connectivity within the dorsal attention network after training (Astle et al., 2015). Specifically, they reported that functional connectivity between the dorsal

attention network and left superior parietal lobe increased after training and correlated with improvements in working memory. The dorsal attention network is widely accepted to be involved in the top-down allocation of attention to locations or features (Vossel et al., 2014). Within the network, the frontal eye fields and intraparietal sulci contain retinotopic maps of the contralateral space (Silver and Kastner, 2009), highlighting their potential significance for visual working memory (Jerde et al., 2012), which was predominantly trained in the Cogmed group. Working memory training may have improved children's performance on working memory tasks through attentional mechanisms, whereby the repeated co-activation of fronto-parietal regions during training enhanced connectivity and attentional control (Astle et al., 2015). Indeed, neurofeedback studies have shown that directly manipulating fronto-parietal activity increases functional connectivity within the network and can improve working memory performance (Shen et al., 2015; Zhang et al., 2013, 2016).

Improvements in working memory after training were also significantly associated with increased activation in the left middle frontal gyrus on a complex span task (the Odd-One-Out). This effect was significant in the adaptive working memory training group but not the non-adaptive control group. To our knowledge, this is the first controlled investigation to demonstrate that improvements in working memory after training are associated with changes in local brain activity in childhood. Whilst we acknowledge that this does not imply causation, greater increases in left middle frontal activation were observed in the adaptive training group relative to the non-adaptive control group, but this was not significant after a Bonferroni correction for multiple comparisons across the four ROIs. Similarly, the adaptive training group showed greater activation in sub-threshold clusters within the bilateral middle frontal gyri in exploratory analyses (see Supplementary materials). This corresponds with findings in adults, where a meta-analysis found increased activation of the dorsolateral prefrontal cortex (overlapping with the middle frontal gyrus) in longer interventions (>2 weeks) and compared

to a control group (Salmi et al., 2018). Increased middle frontal activation has also been observed in adolescents with and without ADHD after training (Stevens et al., 2016). However, this study reported widespread activation increases and may have been related to test-retest effects because there was no control group. We find that activation increases are much more localised when the active ingredients of working memory training are isolated. Taken together, our findings suggest that improvements in children's working memory after training are associated with greater engagement of the left middle frontal gyrus and may explain why the only other controlled investigation in children found no change in behaviour or brain activation (Kelly et al., 2020).

Our findings provide support for functional neuroplasticity in children following working memory training. The repeated activation of fronto-parietal networks during training may increase their activity and connectivity over time thereby affording greater performance on working memory tasks. Similar neural mechanisms have been reported for learning spatial routes, whereby hippocampal activity and functional connectivity changed with training (Keller and Just, 2016). This study further demonstrated that training led to short-term changes in hippocampal white matter diffusivity, a measure of structural connectivity, which correlated with behavioural improvements. Although we show no evidence that working memory training alters structure in grey matter volume, largely consistent with child (Kelly et al., 2020) and adult studies (Metzler-Baddeley et al., 2016), there is good evidence that cognitive training alters white matter connectivity from a recent meta-analysis of adult studies (Kristensen et al., 2018). Future work should seek to establish how alterations in brain function as a result of working memory training are related to alterations in structural connectivity.

Concerning strengths and limitations of the current investigation, a major strength of our study was the examination of multiple neural measures. This is particularly informative since there are very few controlled studies of the neural correlates of working memory training

in children. A limitation of the current study is the use of non-adaptive training, which may have been less challenging and/or engaging. In addition, the non-adaptive control task was notably different to the adaptive working memory training, which involved multiple tasks. The task required updating the verbal contents of memory and it lacked some motivational features, such as feedback on performance, high scores, pleasing thematic graphics, and audio. Despite these differences, behavioural results were very comparable to studies with matched non-adaptive training (Astle et al., 2015; Dunning et al., 2013) and adaptive training on other tasks (Jones et al., 2019), which may better control for expectancy and motivation effects (Shipstead et al., 2012). We also note that the sample had above average IQ and slightly higher than average working memory capacity, which may limit generalisability as baseline ability is known to mediate training effects (e.g. Rennie, Zhang, et al., 2020). Future studies will require larger and more diverse samples to investigate whether neural correlates differ in children with low, average, and high ability.

To conclude, we report novel and robust evidence for functional neuroplasticity in typically developing children following working memory training. Working memory training increased functional connectivity within the dorsal attention network and greater working memory improvements after training were associated with increased recruitment of the left middle frontal gyrus on a complex span task. Repeated activation of fronto-parietal regions involved in attentional and executive control during training may increase their activity and connectivity over time enabling greater performance on working memory tasks. However, it is unclear whether these cognitive benefits extend beyond tasks that are similar to the training. Future work is required to explore whether training-related changes in brain function are linked to ecological outcomes (e.g. performance at school), alterations in white matter connectivity, and individual differences.

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